Managing and Preventing Opioid Misuse Among Patients with Chronic Pain: A Systematic Review of Five Strategies

By

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Abstract

Chronic nonmalignant pain is a common problem that is difficult to treat. Opioids are often used to treat chronic pain, but a significant potential for misuse exists. Adding to this difficulty is the problem of differentiating between untreated pain and drug-seeking behavior. A number of strategies are recommended by different clinical guidelines to help the clinician reduce the potential for opioid misuse among chronic pain patients. These include treatment agreements, urine drug testing, case management, referral to pain specialists, and prescription drug monitoring programs (PDMPs). The purpose of this study was to evaluate the evidence for these strategies in reducing the prevalence of opioid misuse among chronic nonmalignant pain patients. A systematic review was performed and a total of 22 articles were reviewed in detail, of which 5 were included in the final review—1 for treatment agreements, 2 for urine drug testing, 0 for case management, 1 for pain specialists, and 1 for PDMPs. Results showed that treatment agreements are associated with a prevalence of opioid misuse of 13% after five years, urine drug testing decreases the prevalence of prescription drug abuse by 8.8% and illicit drug use by 6%, specialized pain treatment programs reduce reliance on opioid medications as well as indices of addiction, and that the presence of a PDMP slows the rate of increase in state supply of opioids. Proactive PDMPs are associated with further slowing of the rate of increase when compared to reactive PDMPs. In conclusion, research is lacking that evaluates the effectiveness of these strategies, and some of the research that exists is of fair or poor quality. Inferences can be made by evaluating the effectiveness of these interventions in other populations, but the external validity when applied to chronic nonmalignant pain populations is difficult to ascertain. Much further research is needed to evaluate the effectiveness of these strategies to reduce the prevalence of opioid misuse among chronic pain patients.

Introduction

Chronic nonmalignant pain is a common problem that is difficult to treat. Studies have estimated the prevalence of chronic pain at anywhere from 19% to 46.5% in the general population.[1,2] Not all persons who report chronic pain will have pain severe enough to see a healthcare provider, but this pain may still be debilitating. Chronic pain affects many aspects of life, including ability to function and psychological health as well as social and economic well-being. Because chronic pain affects so many aspects of life, treatment of chronic pain often requires a multidisciplinary approach which addresses issues such as pain status, functional status, mental health, ability to sleep, and social relationships.[3]

Opioids are often used for pain control in the treatment of chronic pain patients. However, the potential (and desire) to misuse opioids in clinical settings and the general population is high. Results from the National Survey on Drug Use and Health show that abuse of OxyContin (a long-acting opioid) has increased from 1.9 million abusers in 2002 to 3.1 million in 2004 (an increase of 63% in two years), with the largest increase occurring in young adults aged 18 to 25.[4] Researchers are learning more about this increasing trend by identifying risk factors for misuse from patient demographic data. These findings will allow providers to identify high risk populations and increase vigilance accordingly.

Many different groups have published guidelines to assist primary healthcare providers in treating chronic pain. These groups include health care agencies such as Department of Veterans Affairs,[5] quality improvement organizations such as the Institute for Clinical Systems Improvement,[3] and regulatory agencies such as the Federations of State Medical Boards and many of its members, including the North Carolina Medical Board.[6] The guidelines recommend that certain strategies be implemented to improve outcomes related to pain and to reduce the risk

of opioid misuse. Several of these strategies include treatment agreements (otherwise known as pain contracts), regular urine drug testing (to determine (a) whether the patient is actually taking the prescribed opioid and (b) whether the patient is abusing illicit drugs in addition to the prescribed opioid), case management (to reduce the risk of misuse as well as addressing social aspects of patient care), utilization of a prescription drug monitoring program when available, and when management has become problematic, referral to a specialized pain clinic.

Evidence for the benefits of these strategies on patient outcomes is limited. These strategies are recommended largely based on expert opinion, with the expectation that they will improve important outcomes--including patient-centered outcomes (pain control, functional status, mental health status) as well as public health outcomes (reduction of opioid misuse). While some of these strategies explicitly focus on improving the patient-centered outcomes, others of these strategies are primarily implemented to protect the physician as well as the society from giving prescription drugs to patients who misuse them. The goal of this systematic review is to review the existing evidence for these strategies (urine drug testing, treatment agreements, case management, specialized pain clinics, and prescription monitoring programs) in the reduction of opioid misuse, and to suggest areas for further research.

Background

Burden of Suffering

Chronic nonmalignant pain places a large disease burden on the population. A survey of 46,394 participants over 18 years in 16 different European countries found the prevalence of chronic pain to be 19%.[2] Another survey of 2012 Canadians found the prevalence to be 29% in the general population.[7] The social costs of chronic pain are high as well: among the subjects

with chronic pain in the Canadian sample, almost one-half were unable to attend social and family events.[7] A cross-sectional survey of 28,902 working adults in the United States found that 13% of the total workforce experienced a loss in productive time during a 2-week period due to a common pain condition (headache, back pain, arthritis pain, or other musculoskeletal pain). The loss in productive time was estimated to cost 61.2 billion dollars per year. Three quarters of the lost productive time was explained by reduced performance at work rather than work absence.[8] The authors comment that, with this study design, they may have underestimated current lost productive time among those with persistent pain problems (e.g. chronic daily headache), because of these individuals' ability to adjust their perceptions over their performance over time.[8]

Types of Pain and Non-opioid Treatment Options

Chronic pain conditions envelop a wide variety of diseases with differing pathophysiology and are conventionally differentiated by subtype of pain. Subtypes include neuropathic pain (including diagnoses such as diabetic neuropathy, complex regional pain syndrome, HIV sensory neuropathy, metabolic disorders, phantom limb pain, Parkinson's disease, multiple scleroses, myelopathies, and post-stroke pain), muscle pain (including fibromyalgia, myofascial pain syndrome, and trauma), inflammatory pain (inflammatory arthropathies, infection, post-operative pain, and tissue injury), and mechanical/compressive pain (low back pain, neck pain, visceral and specific musculoskeletal pain).[3] These conditions are similar in that they lead to debilitating pain and decline in functional status and mental health.

A variety of options exist for the treatment of chronic nonmalignant pain. Medicines to alleviate pain can be prescribed by a healthcare provider, and these are described in detail below.

Also, alternative therapies are common in chronic pain patients, presumably because these patients are not satisfied with the benefits of traditional medicine alone. Acupuncture is one of the oldest of these health practices and has led to the popularity of alternative medicine in our culture. It involves stimulation of tissue with fine needles to restore the normal flow of energy, and has been studied with scrutiny.[3] The 1997 National Institutes of Health consensus statement has supported acupuncture's use as an adjunct therapy for numerous pain conditions.[9] Other avenues of treatment for chronic pain include biofeedback, osteopathic manipulation, chiropractic, cognitive behavioral techniques, psychotherapy, massage, and music therapy.

Alternative medicine use is more prevalent among chronic pain patients than healthcare providers may expect. One survey of 110 patients with chronic tension-type headache reported the prevalence of past use of alternative medicine at 40% of patients (22.7% in the last year). Most of the patients that used alternative therapies did so for the alleviation of headaches (77.3%), and almost 60% of these patients did not inform their doctor about the use of alternative therapies.[10] Many different alternative therapies exist, and medical providers must be proactive in obtaining information about their patients' practices.

Pharmacologic options for treating chronic pain are numerous and depend on the type of pain that the patient exhibits. Two decades ago, most chronic pain was treated with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and sometimes opioids.[3] Today a wide variety of classes of medicines are used for different subtypes of chronic pain. Acetaminophen can be used for mild to moderate pain, and is generally very safe except in patients with advanced liver disease. NSAIDs are indicated for the treatment of mild to moderate non-neuropathic pain, but increase the risk of gastro-intestinal bleeds, renal insufficiency, and even cardiovascular disease. This limits their long-term use. Tri-cyclic

antidepressants (TCAs) are a preferred initial therapy for neuropathic pain, especially in the setting of co-existing insomnia, anxiety or depression. Side-effects include sedation, dry mouth, constipation, urinary retention, and possible cardiac arrhythmias. Other antidepressants (with better risk profiles) are also indicated for the treatment of neuropathic pain, but without the same effectiveness as the TCAs. Anticonvulsants, such as carbamazepine, lamotrigine, and gabapentin are also indicated for certain causes of neuropathic pain.[3] Recent advances in the treatment of chronic pain have made the classification of pain subtype an imperative for providers.

Effectiveness of Opioids for the Treatment of Chronic Pain

Opioids have demonstrated limited effectiveness for pain control in the treatment of chronic pain. A well-done randomized trial that examined the use of oral morphine for chronic non-cancer pain of musculoskeletal or soft tissue origin found that a nine-week course of oral morphine improves pain scores with a low risk of addiction.[11] A meta-analysis of opioids in chronic non-cancer pain (80% of patients with nociceptive pain, 12% with neuropathic pain, 7% with fibromyalgia, and 1% mixed) also found that opioids lead to a decrease in pain.[12] However, a recently published systematic review of the effectiveness of opioids for chronic low back pain found that opioids may be effective for pain in the short-term, but that long-term efficacy is unclear.[13]

The effectiveness of opioids in the improvement of functional status is more controversial. The randomized controlled trial mentioned above found that opioids did not provide any significant improvement in functional or psychosocial outcomes.[11] Also, the meta-

analysis of opioids in chronic non-cancer pain found that opioids had less effectiveness in the improvement of functional status than other drugs (diclofenac was specifically mentioned).[12]

In many of the trials in both reviews mentioned, patients with a history of addiction are excluded from the study, making the results of the reviews apply more to efficacy than to effectiveness. Also, many of the trials did not include measures to evaluate the incidence of addiction or opioid misuse, and those that did had short study durations. In summary, consensus exists about the ability of opioids to reduce pain, but the benefits of opioids for other outcomes (specifically functional ability and mental health) have not been rigorously established. This is an important distinction, because many authorities on chronic pain consider functional outcomes of greater importance than improvements in pain scores.

Adverse Effects of Opioid Therapy

Opioid therapy for chronic nonmalignant pain entails a high likelihood of adverse effects. In a sample of 1009 primary care patients taking opioids for chronic nonmalignant pain, patient reported side-effects include constipation (40%), sleeping problems (25%), loss of appetite (23%), and sexual dysfunction (18%).[14] Other adverse effects of opioid therapy include nausea and vomiting, sedation, cognitive impairment and respiratory depression. Many opioids cause an elevation in mood (euphoria) and the reduction of emotional distress,[15] increasing their potential for abuse. Tolerance may occur with opioid use, leading to withdrawal symptoms when discontinued. Concern exists about the possibility of addiction to opioids, characterized by a psychological dependence on the use of the substance, which manifests itself in aberrant behaviors such as loss of control over drug use, compulsive drug use and continued use despite harm.[16] Estimates of addiction rates among patients with chronic non-cancer pain range from 3.2

to 18.9%.[16] Whether these addictions are iatrogenic (that is, whether these are new substance abuse disorders in opioid naïve patients) is unclear.

Opioid Misuse

"Misuse" is a comprehensive term that includes all unsafe practices relating to the use of a certain drug. Often this requires going against the physician's explicit instructions for the use of the medication. In the case of opioids, misuse refers to more than just abuse of the drug—it includes practices like selling the prescription opioid (i.e. diversion) and using illicit drugs while taking the opioid for pain. Ives et al. have formulated the following definition of opioid misuse: negative urine toxicological screening (the patient is not taking their prescription), inconsistent urine screening (positive for other opioids not prescribed by the healthcare professional), doctor collecting (the patient is receiving prescriptions from multiple providers), evidence of diversion, prescription forgery, or urine screening positive for stimulant drugs (cocaine or amphetamine).[17] These practices are usually defined and prohibited in the treatment agreement between the provider and the patient.

More commonly encountered than patients with iatrogenic addiction are patients with pre-existing substance misuse disorders who present to their provider requesting opioids. A one year prospective cohort study of 196 chronic pain patients showed that strong predictors for opioid misuse included self-reported histories of previous alcohol abuse, cocaine abuse, or previous drug or alcohol related criminal convictions.[17] Therefore, one can infer that chronic opioid use does not lead to iatrogenic substance abuse disorders, but that opioids are misused among the patients with pre-existing substance misuse disorders or behaviors. Interestingly,

gender, race, literacy, disability, and measures of socioeconomic status were not associated with misuse in this study.[17]

The potential for misuse with opioids is significant, since patients may be tempted to increase doses either to self-medicate pain or to induce euphoria. The prevalence of opioid misuse among patients at tertiary pain clinics ranges from 3% to 19%.[18] A systematic review found even higher prevalences (up to 24%) of substance abuse and aberrant drug-related behavior among the chronic pain patients in the reviewed studies.[13] Results from the 2004 National Survey on Drug Use and Health (NSDUH) show that 11 million adults per year are abusing prescription opioids.[4]

Because of the diversion of medication, many of those abusing opioids are probably not the same people for whom the prescriptions are being written. For example, opioid prescription misuse is a growing problem in the college community, presumably from diversion of medication by those for whom the prescriptions were written. Estimates of opioid use range from 0% at the lowest risk universities to 20% at the highest risk universities.[19] The 12-month prevalence of any non-medical prescription drug use has more than doubled between 1993 (4.41%) and 2001 (9.97%).[20] Trends in marijuana use were highly correlated with trends in non-medical prescription drug use.

Strategies to Reduce Opioid Misuse

Healthcare providers need tools to mitigate the misuse of prescription opioids. That is, they should prescribe opioids with the reasonable assurance that they are maximizing therapeutic benefit to the patient and minimizing harm. In addition, opioid prescribing is unique in that the

potential for harm may not only accrue to the individual patient but also society at large by abetting the epidemic of prescription drug abuse.

This is a difficult task, because restriction of opioids must be balanced with adequate pain control. To complicate matters, drug-seeking behaviors can either be a sign of addiction or they can point to self-management of under-treated pain.[21] Tools that will be evaluated in this review include urine drug testing, treatment agreements, case management, specialized pain clinics, and prescription monitoring programs. These tools have two main goals: to improve the outcomes of patients with chronic pain,[21] and to prevent drug-seeking individuals without legitimate pain issues from obtaining opioids. While many different techniques are available to predict drug-seeking behavior,[22] distinguishing drug-seeking behavior from legitimate pain can be difficult in clinical practice. In one emergency department study, 22% of patients suspected of drug-seeking behavior were ultimately diagnosed with organic pathology.[23] In light of this diagnostic dilemma, these strategies are intended to be applied non-discriminately to any patient presenting with chronic pain symptoms. This review will focus on evidence for the reduction of opioid misuse in chronic pain patients, regardless of the legitimacy of the pain.

Treatment Agreements. Treatment agreements, otherwise known as pain contracts, are put in place to set clear boundaries and responsibilities for the chronic pain patient. The contract between the patient and the provider usually is based on four distinct assumptions: the terms and consequences for breaching the contract are stated explicitly; the doctor and patient each have unique responsibilities; the doctor/patient relationship is a consensual one (rather than obligatory) and; both physician and patient are willing and able to negotiate.[24] A survey of 39 different contracts from nationally reputed academic medical centers found that most opioid

agreements opioid agreements ranged in length from 1 to 10 pages, encompassing a wide variety of information. Most included information about terms of treatment (97%), prohibited behavior (95%), and points of termination (92%). A large proportion of agreements also included information about patient responsibilities (85%), education (79%), and additional treatment (74%). Information that was present in only a minority of opioid agreements included information about emergency issues (38%), goals (38%), limitations on prescriptions (38%), legal considerations (33%), discouraged behavior (31%), and staff responsibilities (18%).[25]

It can be argued that the opioid agreement is enacted primarily to protect the physician from drug seeking behavior and legal consequences of aiding this behavior. Still, a survey of physicians in Wisconsin found that written drug agreements are only utilized by 42% of primary care practitioners.[26] Any evidence that the accountability provided by treatment agreements reduces the incidence of opioid misuse by chronic pain patients will encourage more physicians to implement this tool. As of 2001, no standardized validated opioid agreement has been put in place,[25] which may make evaluation of the opioid agreement difficult.

Urine Drug Testing. Urine drug testing is an important tool for the measurement of opioid misuse or illicit drug abuse among chronic pain patients. Although urine drug testing is a measurement tool, it also serves as an intervention tool by providing the patient with accountability. If the patient is periodically screened for evidence of opioid misuse, the likelihood that he or she will misuse opioids may decrease. In this way, urine drug testing serves to reinforce the treatment agreement by giving the provider information about the patient's behavior. Evidence of opioid misuse with urine drug testing may include lack of prescribed opioid in urine (indicating that the patient may be diverting or otherwise misusing the opioid) or

presence of an illicit drug in the urine (which also constitutes misuse of the opioid and a breach of the treatment agreement).

Abnormal urine screens among chronic pain pains have been remarkably high in some studies. For example, a retrospective analysis of 470 chronic pain patients found that 45% of patients had an abnormal urine screens.[27] Despite the high prevalence of abnormal urine screening results, urine screening is relatively underutilized. The previously mentioned survey of physicians in Wisconsin found that urine drug testing is only utilized by 8% of primary care practitioners.[26] If these practitioners feel that they can perceive misuse based on behavioral signs alone, they are mistaken. One study showed that 21% of patients with no behavioral signs of drug-seeking behavior had unauthorized drugs in their urine.[28]

Case Management. Case management is emerging as a new tool for the evaluation and effective management of chronic pain patients at high risk for opioid misuse. Case management has been advocated by pain specialists for certain high-risk subpopulations of chronic pain patients.[29] The role of case management has been well established with the use of methadone in addiction treatment programs,[30] but the role in chronic pain patients is relatively unstudied. These populations may have similarities in that addicted populations may seek opioids by presenting with chronic pain symptoms. Even in those patients with legitimate chronic pain issues, case management could provide a unique opportunity for patient education and accountability. Case managers are in a strategic position to assess whether certain patient behaviors are indicative of addiction or of legitimate pain control.[31]

Pain Specialists. Specialized pain clinics offer a wide range of expertise and tools to treat the chronic pain patient. Proponents of pain clinics cite a lack of information among general practice physicians and a lack of proper facilities for treatment as the reasons for the need for more pain clinics.[32] Goals of specialized pain clinics include decreasing the amount of pain the patient experiences, to decrease the amounts and types of medicines that the patient uses, to help the patient attain maximal functional status, to decrease the use of medical facilities and the associated costs, and to help the patient develop insight into the patient's situation.[33] Two out of five of the goals mentioned are concerned with the independence of the patient from the medical system, which may be correlated with a reduction of the prevalence of opioid misuse among chronic pain patients. Any evidence that pain clinics are effective in reducing the incidence and prevalence of opioid misuse would provide more support for referral to pain clinics.

Prescription Drug Monitoring Programs. Prescription drug monitoring programs (PDMPs), or controlled substance reporting systems, represent a public health approach to target the reduction of opioid misuse. As of May 2005, at least 28 states have established or are in the process of establishing prescription monitoring programs for controlled substances.[17] The goals of prescription monitoring programs involve education of the public, delivery of information to pharmacists and providers, execution of public health initiatives to prevent abuse and diversion, and investigation and enforcement of abuse.[34] However, in the effort to reduce misuse of opioids, prescription monitoring programs can have a negative effect on the adequate treatment of chronic pain by stigmatizing the patient and placing restrictions on the provider.[34] Collaboration between regulatory and pain management representatives has attempted to address these issues

by better defining the balance between diversion and treatment of pain, educating providers as to the role and context for prescription monitoring programs, and encouraging ongoing dialogue between the groups.[35]

It is important to note that differences exist in the protocols of different PDMPs. Some can be classified as proactive while others are reactive. Proactive PDMPs analyze data to identify and investigate cases, generating unsolicited reports to send to clinicians. Reactive PDMPs respond to requests for investigation from healthcare providers, generating only solicited reports for clinicians.[36] This distinction is important, because the effects of PDMPs in reducing the misuse of opioids may vary depending on the organization of the PDMP.

Position Statements and Clinical Guidelines

The issue of opioids in chronic pain management has generated a great deal of discussion among clinicians and public health officials alike. Many groups have published position statements or clinical guidelines to aid the clinician in the treatment of chronic pain. The American Pain Society and the American Academy of Pain Medicine have worked together to write a position statement[37] focusing on the issue of under-treatment of pain. A position statement of the American Medical Association[38] has the same focus, arguing for the legitimate use of prescription drugs for chronic pain. A statement by the American Society of Anesthesiologists reports that opioid misuse, aberrant behavior and diversion are rare among chronic pain patients, and that while patient monitoring is important, "the use of patient contracts and/or random blood or urine screening for substances has not been shown to improve compliance or reduce diversion."[39]

In addition, a number of guidelines exist for the treatment of chronic pain. Many state Medical Boards (e.g. the North Carolina Medical Board[6]) have put forth guidelines as well as position statements. The guidelines of the North Carolina Medical Board support the use of a written treatment agreement for high risk patients, including responsibilities of urine/serum medication levels screening when requested. Other guidelines have been published by the Institute for Clinical Systems Improvement,[3] the Veterans Health Administration,[5] and individual researchers.[40,41] Many of these guidelines recommend the use of treatment agreements, include provisions for urine drug testing,[3,5,40] alcohol testing[5] and pill counts.[40] These guidelines also make provision for referral of high risk patients to a pain or addiction specialist.[3,5] Most of these guidelines support the practice of a thorough history and physical examination to elucidate any risk factors for opioid abuse, and to confirm the need for opioid therapy.

Ideally, those who author guidelines will process the evidence in a systematic way to make objective recommendations for clinical practice. Often, however, authors rely on expert opinion when evidence is lacking. Expert opinion is not necessarily formed systematically, and can be swayed by connections with stakeholders.[42] This has been especially true for guidelines concerning chronic pain, as their authors have been susceptible to influences from the pharmaceutical companies that produce opioid medications.[43] The validity of guidelines is limited by these potential conflicts of interest as well as the availability of good evidence, and they should be scrutinized carefully.

Purpose of this Review

One of the position statements mentioned recognizes the need for guidelines to "distinguish legitimate medical practice from questionable practice."[37] To what extent are these

clinical guidelines based on evidence? To my knowledge, no systematic review has been done to determine the effectiveness of these strategies. This systematic review will summarize the evidence for the current practices aimed at reducing opioid misuse among chronic pain patients: treatment agreements, urine drug screening, case management, pain clinics, and prescription drug monitoring programs. The evidence will lead into recommendations for further research as well as recommendations for providers and policy makers.

Methods

The plan for this systematic review was developed through consultation with C. Annette DuBard, MD, MPH and Paul R. Chelminski, MD, MPH. Dr. DuBard is working with Community Care North Carolina on a quality improvement initiative targeting the reduction of opioid misuse in Wilkes County, North Carolina. Dr. Chelminski is a faculty member in the Department of Medicine at the University of North Carolina-Chapel Hill. He is an active clinician and has published studies on the prevalence of opioid misuse among chronic pain patients.

Key Questions

In this review, I examined the following key questions:

1. Do treatment agreements reduce the prevalence of opioid misuse in chronic pain patients?
2. Does urine drug testing reduce the prevalence of opioid misuse in chronic pain patients?
3. Does case management reduce the prevalence of opioid misuse in chronic pain patients?
4. Does management by pain specialists reduce the prevalence of opioid misuse in chronic pain patients compared to management by primary care providers?

5. Do prescription monitoring programs lead to a reduction in the prevalence of opioid misuse among chronic pain patients?

Inclusion and Exclusion Criteria

Using the key questions, I constructed inclusion and exclusion criteria for the studies to be included in this review. Only English language articles were included. Both interventional and observational study designs were eligible for inclusion. Articles from any year were eligible for inclusion, up until the date the search was performed (May 8, 2007). Editorials and reviews were excluded, as well as case reports and studies enrolling fewer than 10 patients.

Included studies were limited to those that evaluated misuse of opioids in patients with chronic pain. The patient population included all patients with chronic pain (pain lasting longer than three months). No subtypes of chronic pain were excluded to improve the generalizability of the results. Studies were included whether or not they incorporated the use of a control group. Specific populations that were excluded included patients with acute pain (lasting shorter than three months), and patients enrolled in substance abuse programs. Articles were excluded from the abstract review if the abstract made no mention of the intervention in question (treatment agreements, urine drug testing, case management, pain specialists or prescription monitoring programs). Although the main outcome was the prevalence of opioid misuse, abstracts that made no mention of misuse were still included for full text review, in the event that misuse was measured but not mentioned in the abstract. For case management, any abstract that made mention of a multi-disciplinary approach was included for full review, on the chance that it may include case management as part of the multi-disciplinary approach.

To limit the reviewed articles to those that evaluated the effectiveness of interventions in reducing the prevalence of opioid abuse in chronic non-cancer pain patients, studies were excluded after full text review if 1) they did not evaluate the proposed intervention, 2) they were cross-sectional studies, 3) they did not measure opioid misuse, 4) they had no control group and did not have any baseline data on opioid misuse, or 5) they did not assess the role of the specified intervention independently of other interventions.

Literature Search and Retrieval Process

Databases and Search Terms. MEDLINE was searched by one reviewer for relevant articles using the following search strategy. The search strategy for each of the key questions was developed with assistance from a Health Sciences Librarian. Each of the key questions included the term "(chronic disease OR chronic) AND pain AND ("Analgesics, Opioid"[MeSH] OR Opioids)" for the first search term. This limited the available studies to those that deal with opioid use in patients with chronic pain. Each key question had a different second search term, connected to the first search term by the Boolean operator "AND". For the question of urine drug testing, the second search term used was "(Substance Abuse Detection OR urine toxicology OR "drug testing")". For the question of treatment agreements, "(contracts OR "treatment agreement" OR "medication agreement" OR agreement[ti])" was used. For the question of case management, "(case management OR patient care management)" was used, because these terms were felt to cover all the literature pertaining to case management. For the question about pain clinics vs. primary care practice, "(pain clinic OR pain clinics OR spine clinic OR orthopedics OR specialty)" was used for the second search term. Finally, for the question about prescription drug monitoring programs, the second search term "(prescription OR controlled substance) AND

(monitoring OR reporting) AND (system OR program OR programs)" was used. The search was not limited to English language articles only, but non-English articles were excluded after abstract review. This permitted the assessment of possible language bias, since trials with more positive results are more likely to be published in English.[44] No date parameters were set, but the earliest article in the search results was published in 1976. Also, a hand search was performed using reviews and studies found in the initial searches to locate other articles that may answer the study questions. Experts in the field were consulted to locate further articles not found in the MEDLINE search or the hand search.

Article Selection and Review. One reviewer evaluated abstracts for inclusion or exclusion. If the articles were not excluded based on abstract review, then the full article was reviewed. Studies identified by expert consultation and hand review were also included for full-text review. After full text review, if the article was not found to meet the inclusion criteria, the article was excluded. Relevant information from all articles included in the full-text review was entered into evidence tables: included studies were entered into **Table 1**, and excluded studies were entered into **Table 2.**

Evaluation of Quality and Strength of Evidence

The articles were assessed for quality scope and relevance. Criteria established by Agency for Healthcare Research and Quality[45] were used to grade the strength of each study as good, fair or poor. I graded the quality of each article by assessing the degree to which chance and certain biases were minimized through the study design. To minimize the role of chance, studies would receive a better score if the study population were large. For selection bias, the

study received a good score if initial comparability of groups was good (if a control group was present), and intention-to-treat analyses were performed. For measurement bias, the study was rated well if the measurements of intervention and outcome were equal, valid and reliable. For confounding bias, the study was rated well if selection bias was minimal and the results of the analysis were controlled for potential confounding variables. Because each article was rated by only one reviewer using a non-validated rating scale, the quality ratings of each study should be interpreted with caution.

Results

Flow of Studies through the Review Process

A total of 332 articles were identified for five different questions (excluding duplicates identified for multiple study questions); 18 regarding treatment agreements, 39 regarding urine drug testing, 156 regarding case management, 166 regarding pain specialists, and 10 regarding prescription reporting systems. See **Figure 1** for a flow diagram of studies through the systematic review process. Thirty-nine of these articles were not in English, and most of the non-English articles were identified in the case management and pain specialist searches. Since only a small proportion of the total articles were not in English (10%), I estimated that language bias would not be a significant issue.

A large proportion of identified abstracts were reviews or editorials (166 articles), and these were excluded before full-text review (some of these were reviewed later during the hand search). Also, 26 case reports were excluded. Of the remaining 158 studies, 119 either made no mention of the study question asked by the review because they dealt with a different question

altogether, or dealt with the correct study question but in a different population (patients with acute pain, or patients on methadone in a substance abuse rehabilitation program). A reference list search of pertinent reviews and studies identified no further articles for full-text review. Expert consultation revealed one not yet published article for full text review evaluating the effect of prescription monitoring programs.

A total of 22 articles, excluding duplicates, were reviewed in full (3 regarding treatment agreements, 10 regarding urine drug testing, 2 regarding case management, 11 regarding pain specialists, and 2 regarding reporting systems). The details of the included studies can be found in **Table 1**,[36,46-51] whereas details about excluded studies can be found in **Table 2**.[17,27,28,46,49,52-65] Nineteen total studies were excluded from the final analysis, from one or more categories (a few of which were included in a different category). For treatment agreements, reasons for exclusion were: 1) the study did not measure misuse (n=1) or 2) the study did not assess the role of treatment agreements independently (n=1). For urine drug testing, reasons for exclusion were: 1) no follow-up (n=4), or 2) no control group or baseline misuse data to assess the effectiveness of urine drug screening (n=4). Those studies that did assess urine drug screening over time reported the incidence of opioid misuse over a block of time, rather than the prevalence at the beginning vs. the prevalence at the end (a pre-post design[66]), which would be helpful to determine whether urine drug screening is actually effective in reducing the prevalence of opioid misuse. For case management, reasons for exclusion were: 1) the study did not assess the role of case management (n=2). For pain specialists, reasons for exclusion were: 1) misuse was not measured as an outcome (n=5), 2) no follow-up (n=1), 3) pain specialists were not evaluated independently (n=1), or 4) no control group or baseline data were available to evaluate the effectiveness of the intervention in reducing the prevalence of opioid misuse (n=3). Finally, for prescription

monitoring programs, reasons for exclusion were: 1) the study did not assess the role of prescription monitoring programs (n=1).

In the end, five studies were included in the systematic review: one uncontrolled study evaluating treatment agreements, two prospective historically-controlled studies evaluating the effectiveness of urine drug testing in reducing opioid misuse, one uncontrolled study evaluating pain specialists, and one ecological study evaluating the effect of prescription drug monitoring programs in twenty states. No studies were included for the effectiveness of case management in reducing the prevalence of opioid misuse.

Treatment Agreements

One uncontrolled study was identified[46] that evaluated the incidence of opioid misuse in chronic pain patients who signed treatment agreements with their providers. Hariharan et al. recorded treatment agreement outcomes over five years in 330 patients with chronic pain who were started on long-term opioids. Over the five years, only 17% (n=54) of contracts were cancelled by the physician. Broken up by subgroup, 8% (n=27) of contracts were cancelled due to positive urine toxicology screening, 4% (n=14) due to prescription drug abuse, 1% (n=4) due to contract rules violations, and 3% (n=9) due to administrative reasons such as transfer of care to a specialist. Only 42% of patients had any urine drug screening performed; of this sample 38% tested positive for illicit drugs. Urine drug screening was more likely to be used in patients who were male, young, or who were taking long-acting or combination (short- and long-acting opioid used in combination) therapy. Urine drug screening was less likely to be used in patients with degenerative joint disease. The study does report that opioid misuse was significantly associated with male gender and combination therapy.

This study's quality was rated as fair. The lack of a control group makes any effect of the treatment agreement difficult to quantify. Also, the inconsistent use of urine drug screening may bias the associations found in the study. For example, opioid misuse was associated with male gender and combination therapy, but urine drug screening was performed more often in these groups. This leads to a measurement bias because the use of testing is not equal in different groups. Still, the investigators should not be faulted for this measurement bias, because the use of urine drug screening was not controlled by the investigators (it was an outcome in and of itself). From these data, one can now predict the likelihood of a physician to use urine drug screening in the context of a treatment agreement.

Urine Drug Testing

Two articles were identified[47,49] that evaluated the effectiveness of urine drug testing in reducing the prevalence of opioid misuse among chronic pain patients and compared the results to controls. Laxmaiah Manchikanti is the primary author of both articles. The patient demographics are identical in both studies, indicating that the two articles appear to be different reports from the same data. The patient population included 500 consecutive chronic pain patients on opioids. One of the articles reports the effectiveness of adherence monitoring (including urine drug testing) in reducing controlled substance abuse[47] compared to historical controls.[48] The other focuses on the reduction of illicit drug use,[49] compared to a different historical control.[50] Both of these outcomes—controlled substance abuse and illicit drug use—are included in the definition of opioid misuse[17] used by this review.

The former article[47] reports a 50% reduction in opioid abuse with the institution of adherence monitoring, which includes treatment agreements, periodic urine drug testing and pill

counts. This corresponds to an absolute decrease in opioid abuse of 8.8% (prevalence of 17.8% in the control and 9% in the intervention). The control group consisted of 500 patients from a previous study[48] in 2003 which did not incorporate the use of urine drug screening or pill counts. The investigators found that, out of the 9% who abused opioids, 5% did so by doctor shopping (i.e. requesting prescriptions from multiple providers), and 4% did so by illegal acquisition through drug trafficking. Even though the intervention in this trial included treatment agreements as well as urine drug testing, the referenced control group[48] included the use of treatment agreements. Therefore, any effect of the intervention should be attributed primarily to urine drug testing and pill counts.

The latter study[49] reports that adherence monitoring reduces the prevalence of illicit drug use from 22% in the historical control to 16% in the intervention group. The historical control consists of 400 consecutive patients from a previous study[50] in 2005. Of note, participants in the control group also received urine drug screening. Out of the 16% illicit drug users, 11% abuse marijuana, 5% abused cocaine, and 2% abused methamphetamine or amphetamines. In subgroup analysis by insurance status, they also report a statistically significant decrease in illicit drug use among the Medicaid population (22% compared to 39% in the control), most prominently in the form of decreased marijuana use (16% compared to 34% in the control).

Using the AHRQ guidelines,[45] I rated the quality of the prescription drug abuse study as fair, and the illicit drug use study as poor. Patient comparability is good in both studies, except in the distribution of different types of insurance in the illicit drug use study. Also, data for experimental and control groups are taken from different studies, which may introduce some bias. In both cases, the investigators report that the study design is prospective, but the length of the study is unspecified. If the data were collected during only one patient visit, this would call into

question the effectiveness of the intervention. Also, the frequency of random urine drug screens is unspecified, so the point at which urine drug testing data are obtained is unclear.

In the study that examines the effect of urine drug testing on illicit drug use, the investigators compare the effects of the intervention[49] to a control group[50] in which patients also gave consent to the use of random drug monitoring through urine drug screening. If the intervention were present to the same degree in both the experimental group and the control group, one would not expect to see much of a difference in outcomes between the two groups. Regardless, any reduction in the prevalence of illicit drug use in the experimental arm should not be attributed to the intervention, but rather to chance or to some other difference between the two groups.

For this reason, the illicit drug use study's quality was rated as poor. Since urine drug testing was performed in both groups, determining the cause of the decrease in prevalence is difficult. Part of this difference could be explained by a difference in representation of the subgroups. The experimental group contained a higher proportion of Medicare recipients (with a lower prevalence of illicit drug use) than did the control group. Also, the experimental group contained a lower proportion of Medicaid recipients (with a higher prevalence of illicit drug use) than did the control group. Both of these situations would lead to an underestimation of the total prevalence of illicit drug use in the experimental group.

Pain Specialists

One uncontrolled study was identified[51] that evaluated the effectiveness of a specialist program over time. Currie et al. measured the effectiveness of a ten week integrated pain management program for recovering substance abusers. The program consisted mostly of

cognitive-behavioral therapy with elements of substance abuse education and relapse prevention. Two professionals facilitated the discussions: an occupational therapist and a family physician, both experienced in chronic pain and addiction medicine. Patients were referred to the program if they had a chronic pain condition and a concurrent diagnosis of substance abuse or substance dependence. The definition of substance dependence accepted by the investigators included many behaviors classified under opioid misuse: e.g. consuming more medication than prescribed, combining opioids with other drugs for pain relief, obtaining prescriptions from multiple providers, or buying opioids from others.

At baseline, 91% of participants had a diagnosis of substance dependence and 9% had a diagnosis of substance abuse. Behaviors were assessed at baseline using the Addiction Severity Index and supplemental questions derived from the Diagnostic and Statistical Manual-IV. Over a 12 month follow-up, patients showed improvements in many Addiction Severity Indices, including medical, psychological, and employment indices. Some of these indices included "days with medical problems" (23.8 out of 30 days at baseline, compared to 19.2 out of 30 days at 12 months), "days with psychological problems" (17.4 out of 30 days at baseline, compared to 12.9 out of 30 days at 12 months), and "concern about employment problems (0-4)" (1.7 out of 4 at baseline, compared to 0.9 out of 4 at 12 months). Opioid use decreased over the course of follow-up (68% at pre-treatment, 59% at post-treatment, 52% at 3 months, and 50% at 12 months).

This study was rated as fair. The absence of a control group allows for confounding bias when analyzing the results. However, because participants were referred to this program because they could not solve their problems independently, one could assume that a control group would show no improvement over the 12 month study period (or perhaps a decline in the

measured indices). Selection bias is a concern, because the study had a large drop-out rate (34%) which consisted mostly of people who developed problems with the treatment program. This bias was minimized by obtaining follow-up data for a proportional number of drop-outs from the program. The major limitation of this study that elicited a rating of "fair" was that follow-up data concerning patient addiction measures relied on self-report rather than objective measures of misuse.

Prescription Drug Monitoring Programs

One article was identified[36] that dealt with the effectiveness of prescription drug monitoring programs (PDMPs) in reducing the abuse of schedule II drugs, including opioids. This manuscript, by Ronald Simeone and Lynn Holland, was not yet published at the time of this review; the article was obtained with the help and permission of Kay Sanford, MSPH, in the Injury and Violence Prevention Branch of the North Carolina Department of Health and Human Services, Division of Public Health. The study uses an ecological study design comparing states with a PDMP to states without a PDMP.

At the time of the study, prescription drug monitoring programs were in place in twenty states. Data from states without prescription monitoring programs were used as a control group to compare six year trends. The investigators reported the relationship between PDMPs and prescription drug abuse using both an indirect and a direct channel. The indirect method involved comparing over six years (1997-2003) the supply of Schedule II drugs in states with PDMPs to states without PDMPs. They argue that decreasing the supply of prescription drugs reduces the probability of abuse. Using data from Automation of Reports and Consolidated Orders System (ARCOS), they found that, although supply of most Schedule II drugs had

increased over the six year interval, the rates of increase were lower in states with PDMPs than in states without a PDMP for all pain relievers except hydromorphone, which showed comparable rates of increase. Also, states with proactive PDMPs have a slower rate of increase in supply than states with reactive PDMPs. The investigators go on to develop a multilevel individual response model which is used to support their hypothesis that prescription drug supply is linked with probability of prescription drug abuse, and consequently probability of admission to a drug treatment program.

The direct method involved using the data from all patient admissions into state-licensed drug treatment programs. Patient admissions data represent only those people seeking treatment for drug abuse, and therefore only catches a small minority of total people with drug abuse problems. This data does not show any significant differences between states with PDMPs and states without PDMPs.

The quality of this study was rated as good. The use of a control group (states without PDMPs) as well as trend analysis reduces the role of bias in the study design. This study clearly shows that the existence of a PDMP is associated with a slower rate of increase in supply of prescription drug supply, specifically Schedule II drugs. By using the multilevel individual response model, they further support their hypothesis that drug supply is closely linked to probability of abuse. The main drawback of this study design is that no data concerning illicit drug use are available, precisely because illicit drugs are illegal in all situations and their supply is not well known. Thus, no information is available for the patients who misuse their opioid prescription by taking illicit drugs concurrently. Also, it is difficult to determine to what extent the chronic pain subpopulation in particular is benefiting from PDMPs.

Discussion

In summary, evidence is scarce for the benefits of treatment agreements, urine drug testing, case management, pain specialists and prescription drug monitoring programs in the reduction of the prevalence of opioid misuse in chronic pain patients. Different investigators have evaluated the effectiveness of interventions over time, but many of these investigations lack both a control group and baseline data regarding the prevalence of opioid misuse.

Based on the limited data available, tentative conclusions can be made regarding four of the five interventions evaluated by this review. Treatment agreements are associated with a prevalence of opioid misuse of 13% after five years (assuming that the prevalence of opioid misuse is 0% at baseline because patients are beginning opioid therapy).[46] Urine drug testing decreases the prevalence of prescription drug abuse by 8.8%[47] and illicit drug use by 6%[49] using historical control groups,[48,50] but the quality of the data is questionable. Specialized pain treatment programs reduce reliance on opioid medications as well as indices of addiction.[51] However, the studied specialist treatment program may be quite different from a typical pain specialist clinic. Unpublished research concerning prescription drug monitoring programs has shown that the presence of a PDMP clearly slows the rate of increase in supply of Schedule II drugs, including opioids.[36] They also show that states with proactive PDMPs have slower rates of increase in supply than states with reactive PDMPs. By using statistical modeling, they argue that an increase in supply leads to an increase in the probability of abuse.[36]

The relationship between supply and abuse is strongly supported by recent work comparing opioid analgesic sales to drug poisoning mortality by state.[67] Significant positive correlations were found between drug poisoning mortality and statewide sales of methadone, oxycodone, and hydromorphone individually. A scatterplot from this research demonstrated a

linear relationship between total opioid sales and mortality from drug poisoning (**Figure 2**), reinforcing the conclusion that an increase in opioid supply leads to an increase in the likelihood of abuse. This conclusion is provocative because—although preliminary—it links physicians prescribing behaviors to deterioration, not amelioration, of an important public health problem.

This review contains notable strengths. First, the search strategies were developed in consultation with a health sciences librarian as well as experts in the field. The breadth of the search strategies was confirmed when different articles recommended by experts in the field were present in the search. Second, this review addresses a number of different strategies for the reduction of opioid misuse. Third, the inclusion of a flow diagram allows the reader to see why studies were excluded, whether because the articles were reviews, studies that did not answer the review question, or articles that were not published in the English language.

This review also has some limitations. The most notable limitation is that abstracts and full-text articles were reviewed by only one reviewer. The involvement of two different reviewers would decrease the role of individual bias in selecting articles. If two reviewers had judged the abstracts, ideally a third person would classify any articles for which the first two reviewers disagreed. The role of individual selection bias was reduced by using strict predetermined inclusion and exclusion criteria. The inclusion of the search strategies as well as a detailed flow diagram of included and excluded studies allows the reader to appraise the quality of the review for him or herself. Another limitation is that the quality of each included article was similarly rated by only one reviewer. This, again, can introduce personal bias. However, important study characteristics were detailed to allow the reader to make his or her own conclusions about the quality of the studies.

As far as I know, this is the first systematic review of its kind that deals specifically with the reduction of opioid misuse among chronic pain patients. A narrative review by Kahan et al.[18] has dealt with the question of opioid misuse, and provided helpful information about the interpretation of urine drug testing, as well as a recommendation to routinely use treatment agreements, to titrate opioid dosing cautiously, and to watch for signs of misuse. The narrative review also confirms that most recommendations regarding identification and management of opioid misuse are based on expert recommendation.

This systematic review contributes to the body of current literature in a number of ways. First, the flow diagram (**Figure 1**) shows us the distribution of literature surrounding these topics. Out of the many articles identified, only five dealt specifically with misuse using a control group or having a pre-post study design. This confirms the lack of available evidence concerning the effectiveness of different interventions to reduce the prevalence opioid misuse among chronic non-cancer pain patients. Also, the two articles dealing with urine drug testing are difficult to use in making any conclusions about urine drug testing, due to methodological flaws and omitted information.

This review has identified new evidence supporting the role of prescription drug monitoring programs. This evidence can be used to recommend the institution of PDMPs in states that do not yet have them. Also, the evidence concerning the difference between proactive and reactive PDMPs may encourage states with reactive PDMPs to make the necessary changes to take a more proactive stance to reduce the prevalence of opioid misuse. This evidence can also be used to encourage clinicians in states with a reactive PDMP: although the system itself does not proactively notify the clinicians about problem patients, the clinician can use the system in a more proactive way. By contacting the PDMP for every chronic pain patient, the clinician

can in effect make the reactive PDMP a proactive one, and one would hope that this would lead to less probability of opioid misuse through reductions in the supply of these drugs.

The implications of this review for future research are several. First of all, more research must be done to quantify the effects of these strategies in reducing the prevalence of opioid misuse. Also, during the process of this review, I came upon well-designed studies that evaluated the effectiveness of different interventions, but did not quantify opioid misuse. For example, Becker et al.[60] performed a randomized trial comparing pain management in a multi-disciplinary pain center to that in a general care practice, but did not include opioid misuse as an outcome. As opioid misuse becomes a more prevalent issue in our society, researchers should make reasonable efforts to include misuse as an outcome in comparative trials. Also, efforts should be made when possible to either include a control group or to quantify baseline opioid misuse. These methods would add valuable information regarding the effectiveness of different interventions to reduce the prevalence of opioid misuse.

The effectiveness of many of these strategies in reducing the prevalence of opioid misuse is still unknown. However, many of these strategies serve other purposes besides preventing opioid misuse. Treatment agreements allow the clinician to protect him or herself by terminating the relationship if the patient demonstrates clear opioid misuse. Although the utility of urine drug testing as an accountability tool to reduce the prevalence of opioid misuse is not well appreciated, it is still useful as a measurement tool. In the same way, primary care physicians refer their patients to pain specialists for reasons other than an opioid misuse problem. While the utility of these strategies in reducing the prevalence of opioid misuse is unknown, they can still be implemented based on other rationales.

Addendum:

What can we infer?

The existing body of literature is limited in addressing the study questions as they were asked by this review. To augment our understanding of the issues involved with these interventions, we can infer conclusions about the effectiveness of different strategies using other studies and related work. Until research is performed that answers these questions directly, the works mentioned below, as well as others, will provide the best available information.

Treatment Agreements. Although no studies were located that evaluated the effectiveness of treatment agreements using a control group, studies without control groups can be compared to data obtained in other studies to gain some understanding about the utility and success of treatment agreements. In the Hariharan study,[46] if we remove those patients whose agreements were cancelled due to administrative reasons, opioid misuse was detected in 13% of patients over five years. This percentage falls within the 3 to 19% range of opioid misuse among patients at tertiary pain clinics reported earlier.[18] These percentages were likely calculated from practices that included treatment agreements as well, making a conclusion regarding the effectiveness of opioid contracts difficult. A noteworthy limitation of the study is that less than 45% of patients received urine toxicology screening, so the total prevalence of opioid misuse using this important tool is probably underestimated. This brings up an important observation: lacking any specific urine drug testing protocol, urine drug testing is likely to be underutilized as a diagnostic tool.

The study does report that opioid misuse was significantly associated with male gender and combination therapy (although urine drug screening was performed more frequently in these groups as well). Thus, although we do not know the overall effectiveness of treatment agreements, we do have some evidence that treatment agreements are more likely to be successful in female patients as well as those patients who are managed on only one opioid medication (although these observations should be confirmed by research with tightly controlled measurement strategies).

This review did not identify any studies in which treatment agreements were instituted after opioid therapy had already begun. Studies could evaluate this by estimating the prevalence of opioid misuse before treatment agreements are instituted, and measuring again after treatment agreements are instituted. This type of study design could provide clear data to show whether treatment agreements have a noticeable effect in decreasing the prevalence of opioid misuse among chronic pain patients.

Urine Drug Testing. While the effectiveness of urine drug testing has not been well studied in the chronic pain population, it may be possible to make some inferences from the literature surrounding random drug testing in other environments.

Urine drug testing in the public school system may provide some interesting inferential hypotheses. While many differences exist between the adolescent population and the chronic pain population, random urine drug testing should have at least one similar effect in both groups: the reduction of illicit drug use. Yamaguchi et al.[68] compared adolescent self-reported illicit drug use to the presence of drug testing in the school. Between the years 1998 to 2001, 18.14% of schools reported using drug testing of any kind. No association was found between the

presence of a drug testing program in the school and the prevalence of self-reported illicit drug use. The lack of association persisted after controlling for various demographic factors. If the chronic pain population responds to urine drug testing in a similar way, we might expect that urine drug testing would not be an effective method to reduce the prevalence of opioid misuse.

However, it is important to note that the drug testing programs in most schools at the time of this study were not actually random. Of the total schools using drug testing (18.14% of total schools), 78% (14.15% of total schools) of schools reported that they only tested due to cause or suspicion.[68] If testing due to cause or suspicion is less effective on a population scale than true random testing, this would bias the results of the study toward the null. Therefore, we may expect that urine drug testing, when applied based on suspicion rather than randomly throughout the chronic pain population, may not have any better effect than that of drug testing in schools. This conclusion has important applications for many healthcare professionals treating chronic pain, since many providers are currently using urine drug testing based on suspicion rather than using random testing.[46]

The use of urine drug testing in the workplace may also offer interesting information. While workplace drug testing is unpopular in the general public and denounced by the American Civil Liberties Union,[69] a recent study of workplace drug testing in the Finnish Defence Forces[70] may provide evidence for its effectiveness. In this setting, workplace drug testing was part of an overall anti-drug strategy, which included public proclamation of zero-tolerance to illicit drugs and emphasis on the importance of the healthy drug-free way of life. While they acknowledge that the publicity of this program may have led to some selection bias in those who applied for positions, they report an amazingly low detection of illicit drug use (only one positive test in

over 2000 samples in four years). They conclude that the anti-drug strategy must be at least partly responsible for findings.

It is difficult to say whether evidence concerning urine drug testing in the school system or in the workplace can be used to infer the effectiveness of testing in chronic pain patients. Many differing factors between the populations may make generalizations difficult. For example, one important difference in the chronic pain population is that the physician is both the supplier of opioids as well as the enforcer of proper adherence practices. In order to truly assess the effectiveness of urine drug testing in the reduction of opioid misuse, it will be necessary to conduct well-designed studies in chronic pain populations, using a standard protocol for the use of random urine drug testing. Future research concerning the effectiveness of urine drug testing should take care to carefully define the methods by which urine drug testing is implemented, as this may have a significant effect on the effectiveness of urine drug testing.

This research may be difficult in the case of urine drug testing, because the intervention is also the method by which outcomes are measured. A study could be designed in which urine drug testing is performed on all patients, but the results would not be available to the physicians of patients in the control group. This distinction would have to be clearly communicated to the patients in each group in order to accurately measure the psychological impact of urine drug testing on patients' decisions. One would hypothesize, then, that opioid misuse would be less prevalent in the group in which urine drug testing results are available to the physician. If this were true, we could show that urine drug testing is not only effective as a measurement tool, but also as an intervention to reduce the incidence of opioid misuse in chronic pain patients.

Case Management. No evidence was found of the effectiveness of case management in the setting of chronic pain treatment. However, case management has been studied in the setting of substance abuse treatment programs. Case management has been shown to be effective in increasing enrollment in substance abuse treatment programs,[71] and in retaining the patients,[72] but does case management help to reduce the prevalence of substance abuse?

McLellan et al.[73] report the benefits of case management in the management of substance abusers in Philadelphia from 1998-2001. During this time, the five largest detoxification programs in the city of Philadelphia identified "Multiple-Detoxification Only" patients (i.e. patients admitted to any detoxification unit three or more times in the past twelve months) and assigned clinical case managers to these patients. 890 patients received clinical case management over the course of the three year intervention. The case managers provided many different services, including assessment, negotiating a service plan, problem solving, contacting agencies and providing transportation. Out of a sample of the first 100 patients who received case management in the third year of the intervention, the researchers found a marked reduction in the number of patients who received detoxification-only admissions (67% to 30%), and increases in the proportion of patients utilizing rehabilitation services (30% to 70%). This implies that the case managers were able to help patients use the healthcare system effectively by utilizing continuity care (rehabilitation) rather than emergency care (admission to a detoxification unit).

One can imagine that these benefits would translate into improved outcomes for chronic pain patients: decreased emergency department utilization, improved use of the chronic pain visit, with decreases in opioid misuse due to improved adherence to the prescribed regimen. However, this inference should be made cautiously for several reasons. First, the intervention in

Philadelphia was uncontrolled, so the exact effect of case management is difficult to determine. Also, it is unclear whether the benefits of case management will be the same in chronic pain patients as they are in substance abuse patients. There may be some overlap in these populations, as some patients with uncontrolled pain may resort to self-medication and eventually become substance abusers and develop substance dependence.

Even if case management is found to be effective in reducing the prevalence of opioid misuse among chronic pain patients, it will be important to discern the optimal level of involvement of the case manager. Recent research in the opioid dependence literature has shown that the efficacy of thrice-weekly medication dispensing and extended weekly counseling sessions did not differ significantly from that of once-weekly dispensing and brief weekly counseling sessions.[74] If the services provided by case managers are found to be beneficial for chronic pain patients, more contact may not improve outcomes to a greater extent.

Pain Specialists. Although finding a controlled evaluation of the effectiveness of pain specialists is difficult, uncontrolled studies can provide important information. To the extent that patients are recruited from practices in which they had received the maximum benefit possible from standard care, patients' baseline data could substitute as a surrogate control group for comparison. In other words, if a patient had been stable in pain control and functional status for many years in a primary care setting, we could assume that the patient had received his or her maximum benefit from customary care. If this patient, who had benefited maximally from standard care, showed improvement in response to the intervention, one could infer that the improvement is a result of the intervention, in much the same way that one could conclude this using a comparison to a control group. However, this type of observation requires some baseline

observation regarding prevalence of opioid misuse, which is difficult because misuse is measured over time. Three such studies were excluded from this review based on the fact that they lacked a control group and could not obtain baseline data, and they deserve some mention here.

Chelminski et al.[53] performed a 3-month study evaluating the effectiveness of a multidisciplinary disease management program in many patient outcomes, including misuse of opioids (using the definition of misuse cited by this review). Physicians were encouraged to refer patients if they were having difficulty managing the patient's pain, or if the physician suspected opioid misuse. In this situation, as above, we can assume that the patient has received the maximum possible benefit from standard care. Therefore, improvements at three months over baseline can probably be attributed to the intervention. The investigators did find improvements in pain, disability and depression scores. However, because the determination of opioid misuse requires observation over time, no baseline status of opioid misuse was available, making inferences regarding the effectiveness of the program in reducing misuse difficult. Over the course of the study, 32% of patients committed some form of serious opioid misuse.

Chabal et al.[54] looked at 403 chronic pain patients in a pain clinic at the Seattle VA Medical Center, 76 of which were on chronic opioid therapy. They defined opioid abuse as: (1) an overwhelming focus on opioid issues by the patient lasting beyond the third visit, (2) pattern of early refills or escalating drug use, (3) multiple telephone calls or visits to the clinic asking for refills or creating a disturbance, (4) pattern of reporting lost, spilled or stolen medications, or (5) supplemental sources of opioids from other providers. Using these criteria, they found that 34% (26/76) of chronic opioid users in this study met one or more criteria, and 28% (21 patients) met three or more criteria. In a one year follow-up of these 21 patients, 3 remained in the VA system

on stable doses of opioids, 4 were being prescribed opioids by psychiatrists not at the pain clinic, and 14 were no longer treated at the VA system (9 of which had completed drug treatment or had legal difficulties over opioid use).

Mahowald et al.[64] evaluated 230 orthopedic spine clinic patients over the course of 3 years for improvement in certain outcomes: improvement in pain, dosage escalations, side effects, and incidence of abuse. They found the frequency of opioid abuse behaviors in long-term opioid users (greater than 3 months) to be 5%. However, opioid abuse was diagnosed by interview only, and the use of urine drug testing was not mentioned as a measurement tool. Given this fact and comparing to estimations in other studies, their estimate of opioid misuse may be artificially low.

New Directions in the Prevention of Opioid Misuse

While the existing body of literature surrounding the topic of opioid misuse is limited, new work is being published rapidly to address this growing problem. Multiple screening tools are being developed to assist the clinician in the assessment of opioid misuse risk. The Pain Medication Questionnaire has shown predictive value for substance abuse, psychopathology, and physical/life-functioning.[75] The Opioid Risk Tool has demonstrated high sensitivity and specificity for determining risk of opioid related, aberrant behaviors.[76] The Addiction Behaviors Checklist is a viable assessment tool to increase a clinician's confidence in determination of inappropriate opioid use.[77] These tools may help the clinician to target certain individuals for higher levels of adherence monitoring. It is important to remember, however, that misuse-monitoring strategies such as urine drug testing may be most effective when administered randomly rather than specifically targeted towards high-risk individuals.

Opioid misuse is a public health problem, affecting the chronic pain population as well as drug addicts. As such, opioid misuse requires a public health answer. The primary care clinicians in contact with the patient cannot be expected to bear the entire burden of managing this problem. The potential role of case management has already been mentioned, as has the role of the state, by gathering data and making it available through prescription drug monitoring programs. Other professionals have a role as well, including pharmacists[78] and nurses.[79] Psychiatrists have also been encouraged to take a more active role in pain management.[80]

Medical school administrations have an important part to play in addressing the problem of opioid misuse. A study of general practitioners in Sweden[81] has shown that physicians experience internal dilemmas when prescribing opioids, concerning the appropriateness of the drug and the concern about abuse and addiction. These dilemmas only rarely led to a denial of an opioid prescription for the patient. The researchers suggest that physicians need more training in saying no to patients, or perhaps better education regarding the proper indications for opioids.

This hypothesis is supported by other research that surveyed a medical school class as freshmen and again as seniors.[82] They found that seniors scored lower on opiophobia scales than they had as freshmen (meaning that they became less reluctant to prescribe opioids, expressed less fear of patient addiction, and expressed less fear of investigation by a Drug Regulatory Agency). However, more than half of the seniors believed patient addiction risks to be substantial, and more than one third expressed fear about investigation. Also, senior students had a more negative attitude towards patients' psychological problems and a more pessimistic outlook on relieving chronic pain. Medical schools have a unique opportunity to engage this issue by devoting time to the education of medical students regarding these issues.

Other public health strategies have targeted inner city drug use. The death rate in Baltimore due to drug intoxication hit a 10 year low in 2006, due to efforts of the city to make drug treatment readily available, and to provide naloxone (an opioid antagonist) to addicts to reverse the effects of opioid overdose themselves.[83] Another group in New York City has done focus group research to elucidate why resistance to using naloxone exists.[84] Efforts to target all users of opioids—whether chronic pain patients or heroin addicts—will be necessary to reduce the prevalence of opioid misuse and deaths that occur as a result. These new techniques, as well as those currently recommended by different guidelines, require further study in order to provide a solid base of evidence for their use.

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Tables and Figures:

Figure 1. Literature Search Flow Diagram

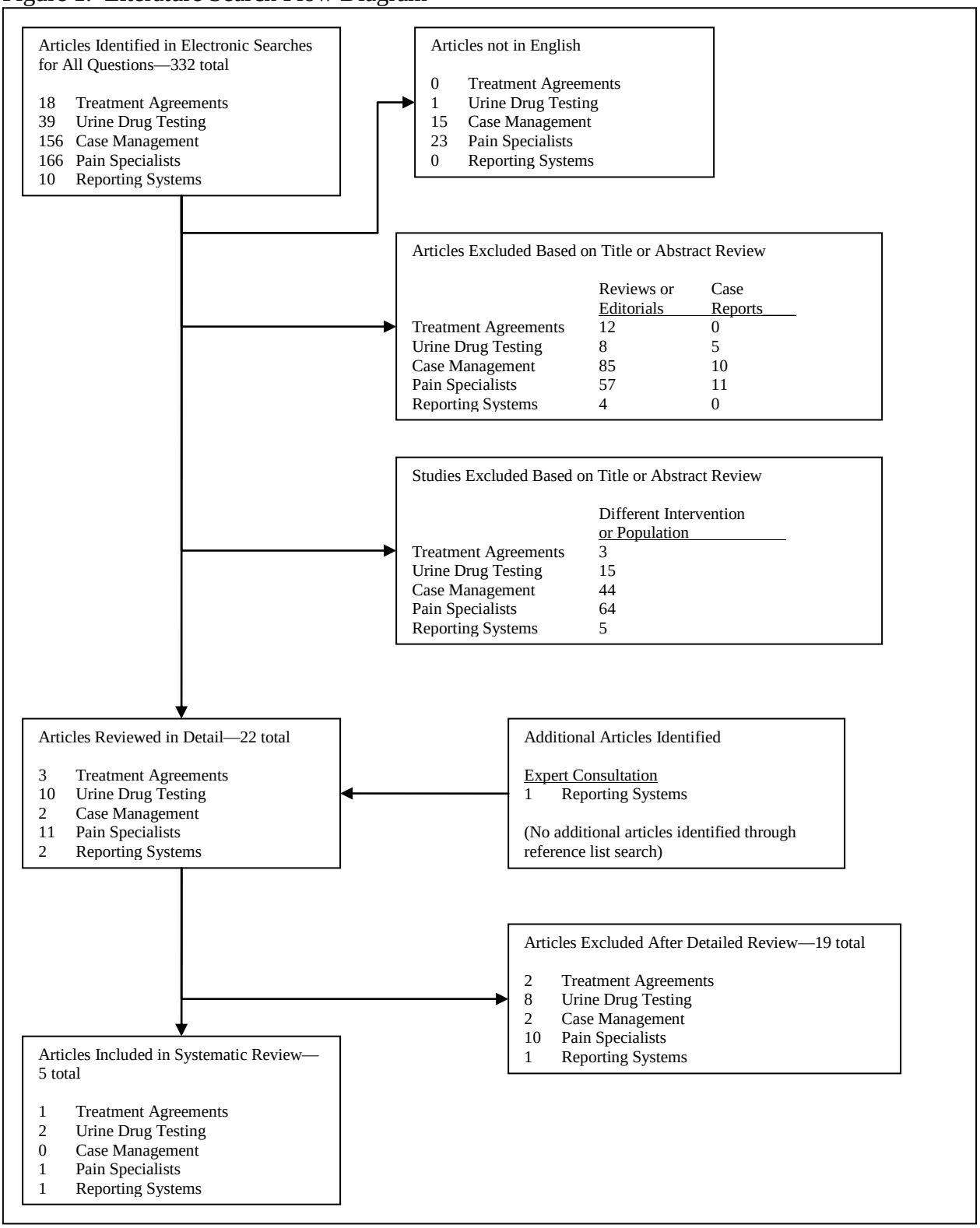

Figure 2. Opioid analgesic sales vs. unintentional & undetermined drug poisoning deaths by state, United States, 2002.[67]